

WHAT IS CLAIMED IS:

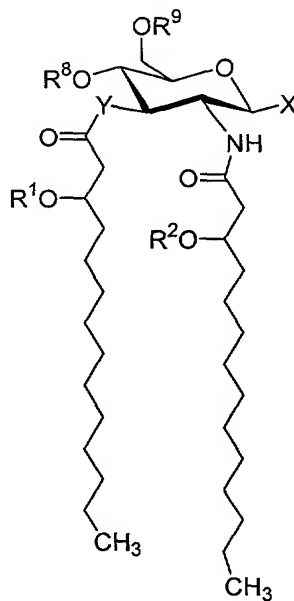
1. An immunostimulant composition comprising:

(a) at least one aminoalkyl glucosaminide phosphate (AGP); and

(b) at least one saponin.

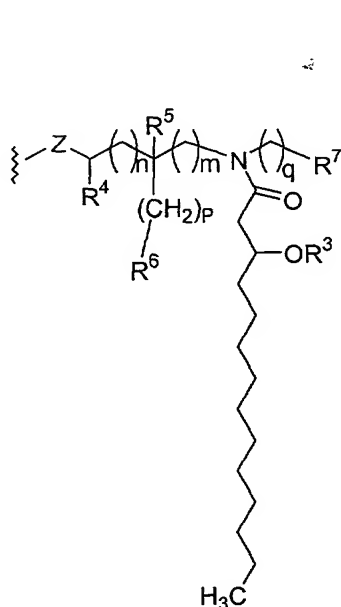
2. The composition of claim 1, wherein the AGP comprises a compound

having the structure:

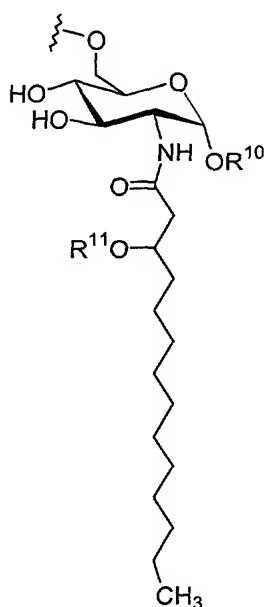


(I)

and pharmaceutically acceptable salts and derivatives thereof, wherein Y is $-O-$ or $-NH-$; R^1 and R^2 are each independently selected from saturated and unsaturated (C_2-C_{24}) aliphatic acyl groups; R^8 is $-H$ or $-PO_3R^{11}R^{12}$, wherein R^{11} and R^{12} are each independently $-H$ or (C_1-C_4) aliphatic groups; R^9 is $-H$, $-CH_3$ or $-PO_3R^{13}R^{14}$, wherein R^{13} and R^{14} are each independently selected from $-H$ and (C_1-C_4) aliphatic groups; and wherein at least one of R^8 and R^9 is a phosphorus-containing group, but R^8 and R^9 are not both phosphorus-containing groups; and X is a group selected from the formulae:

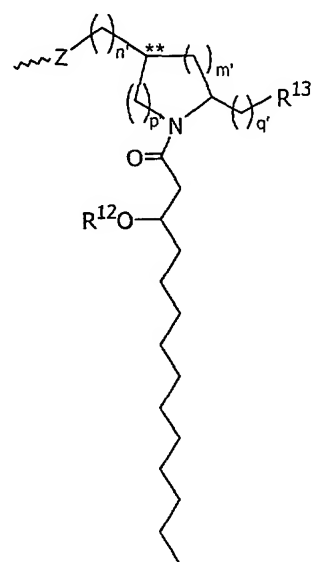


(Ia)



(Ib)

and



(Ic)

wherein the subscripts n, m, p, q, n', m', p' and q' are each independently an integer of from 0 to 6, provided that the sum of p' and m' is an integer from 0 to 6; R³, R¹¹, and R¹² are independently a saturated or unsaturated optionally substituted aliphatic (C₂-C₂₄)acyl group, provided that when X is formula (Ia), one of R¹, R² and R³ is optionally hydrogen; R⁴ and R⁵ are independently selected from H and methyl; R⁶ and R⁷ are independently selected from H, OH, (C₁-C₄)oxyaliphatic groups, -PO₃H₂, -OPO₃H₂, -SO₃H, -OSO₃H, -NR¹⁵R¹⁶, -SR¹⁵, -CN, -NO₂, -CHO, -CO₂R¹⁵, -CONR¹⁵R¹⁶, -PO₃R¹⁵R¹⁶, -OPO₃R¹⁵R¹⁶, -SO₃R¹⁵ and -OSO₃R¹⁵, wherein R¹⁵ and R¹⁶ are each independently selected from H and (C₁-C₄)aliphatic groups; R¹⁰ is selected from H, CH₃, -PO₃H₂, ω-phosphonooxy(C₂-C₂₄)alkyl, and ω-carboxy(C₁-C₂₄)alkyl; R¹³ is independently selected from H, OH, (C₁-C₄)oxyaliphatic groups, -PO₃R¹⁷R¹⁸, -OPO₃R¹⁷R¹⁸, -SO₃R¹⁷, -OSO₃R¹⁷, -NR¹⁷R¹⁸, -SR¹⁷, -CN, -NO₂, -CHO, -CO₂R¹⁷, and -CONR¹⁷R¹⁸, wherein R¹⁷ and R¹⁸ are each independently selected from H and (C₁-C₄)aliphatic groups; and Z is -O- or -S-.

- 34 3 The composition of claim 2, wherein X is a group of formula (Ia).
35
36 4. The composition of claim 2, wherein X is a group of formula (Ib).
37
38 5. The composition of claim 2, wherein X is a group of formula (Ic).
39
40 6. The composition of claim 2, wherein X is formula (Ia) and one of R¹,
41 R² and R³ is hydrogen.
42
43 7. The composition of claim 2, wherein R¹, R², R³, R¹¹ and R¹² are each
44 acyl.
45 8. The composition of claim 3, wherein R¹, R² and R³ are each C₇-C₁₆
46 aliphatic acyl groups.
47
48 9. The composition of claim 3, wherein R¹, R² and R³ are each C₈-C₁₄
49 aliphatic acyl groups.
50
51 10. The composition of claim 3, wherein R¹, R² and R³ are each C₉-C₁₄
52 aliphatic acyl groups.
53
54 11. The composition of claim 3, wherein R¹, R² and R³ are each C₁₀-C₁₄
55 aliphatic acyl groups.
56
57 12. The composition of claim 3, wherein R¹, R² and R³ are each C₁₀-C₁₄
58 saturated aliphatic acyl groups.
59
60 13. The composition of claim 5, wherein R¹, R² and R¹² are each C₉-C₁₄
61 aliphatic acyl groups.
62
63 14. The composition of claim 5, wherein R¹, R² and R¹² are each C₁₀-C₁₄
64 aliphatic acyl groups.
65
66 15. The composition of claim 5, wherein R¹, R² and R³ are each C₁₀-C₁₄
67 saturated aliphatic acyl groups.

- 68
- 69 16. The composition of claim 2, wherein X is oxygen.
- 70
- 71 17. The composition of claim 2, wherein R⁸ is a phosphorus-containing
- 72 group and R⁹ is hydrogen.
- 73
- 74 18. The composition of claim 2, wherein R⁸ or R⁹ is a phosphorus-
- 75 containing group, and R¹¹ and R¹², or R¹³ and R¹⁴, respectively, are both hydrogen.
- 76
- 77 18. The composition of claim 3, wherein the total of $n + m$ is 0, 1, or 2.
- 78
- 79 19. The composition of claim 3, wherein p and q are independently 0, 1 or
- 80 2.
- 81 20. The composition of claim 3, wherein R⁶ is selected from hydrogen,
- 82 hydroxy and carboxy.
- 83
- 84 21. The composition of claim 5, wherein n' , m' , p' and q' are independently
- 85 0, 1 or 2.
- 86
- 87 22. The composition of claim 5, wherein n' is 1, m' is 2, and p' and q' are
- 88 zero.
- 89 23. The composition of claim 22, wherein R¹, R² and R¹² are each C₁₀-C₁₄
- 90 saturated aliphatic acyl groups.
- 91
- 92 24. The composition of claim 23, wherein Y and Z are both oxygen; R¹³ is
- 93 hydrogen; and R¹, R² and R¹² are each C₁₀ saturated aliphatic acyl groups.
- 94
- 95 25. The composition of claim 23, wherein Y and Z are both oxygen; R¹³ is
- 96 hydrogen; and R¹, R² and R¹² are each C₁₂ saturated aliphatic acyl groups.
- 97
- 98 26. The composition of claim 23, wherein Y and Z are both oxygen; R¹³ is
- 99 hydrogen; and R¹, R² and R¹² are each C₁₄ saturated aliphatic acyl groups.
- 100

27. The composition of claim 1, wherein the AGP is a monophosphoryl lipid A.

28. The composition of claim 3, wherein R^1 , R^2 and R^3 all are n - $C_{13}H_{27}CO$; X and Y are both oxygen; n , m , p , and q are each zero; R^4 , R^5 , R^6 , R^7 and R^9 are each hydrogen; and R^8 is PO_3H_2 .

29. The composition of claim 3, wherein R^1 , R^2 and R^3 all are n - $C_{11}H_{23}CO$; X and Y are both oxygen; n , m , and q are each zero; p is 1; R^4 , R^5 , R^7 and R^9 are each hydrogen; R^6 is hydroxy; and R^8 is PO_3H_2 .

30. The composition of claim 1 wherein the saponin is selected from naturally obtained saponins, synthetically obtained saponins, saponin conjugates, saponin derivatives, and saponin mimetics.

31. The composition of claim 1, wherein the saponin comprises a Quillaja saponin.

32. The composition of claim 31, wherein the Quillaja saponin comprises Quil A, QS-7, QS-17, QS-18 or QS-21.

33. The composition of claim 1, wherein the saponin comprises a triterpene saponin-lipophile conjugate comprising a nonacylated or desacylated triterpene saponin that includes a 3-glucuronic acid residue; and a lipophilic moiety; wherein said saponin and said lipophilic moiety are covalently attached to one another, either directly or through a linker group, and wherein said direct attachment or attachment to said linker occurs through a covalent bond between the carboxyl carbon of said 3-glucuronic acid residue and a suitable functional group on the lipophilic residue or linker group.

34. The composition of claim 33, wherein the triterpene saponin (a) has a triterpene aglycone core structure with branched sugar chains attached to positions 3 and 28, and an aldehyde group linked or attached to position 4; and (b) is either originally non-acylated, or requires removal of an acyl or acyloyl group that is bound to a saccharide at the 28-position of the triterpene aglycone

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15 34. The composition of claim 33, wherein said lipophilic moiety comprises
16 one or more residues of a fatty acid, terpenoid, aliphatic amine, aliphatic alcohol, aliphatic
17 mercapton mono- or poly- C₂-C₄ alkyleneoxy derivative of a fatty acid, mono- or poly- C₂-C₄
18 alkyleneoxy derivative of a fatty alcohol, glycosyl-fatty acid, glycolipid, phospholipid or a
19 mono-, or di-acylglycerol.

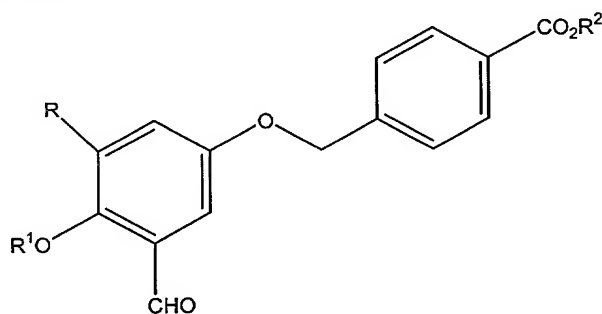
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21 35. The composition of claim 1, wherein the saponin comprises GPI-0100.

22
23 36. The composition of claim 33, wherein said triterpene saponin has a
24 quillaic acid or gypsogenin core structure.

1 37. The composition of claim 36, wherein said desacylsaponin or
2 nonacylated saponin is selected from the group consisting of Quillaja desacylsaponin, S.
3 jennisensis desacylsaponin Gypsophila saponin, Saponaria saponin Acanthophyllum saponin
4 and lucyoside P saponin.

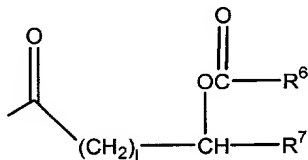
1 38. The composition of claim 1, wherein the saponin comprises a
2 saponin/antigen covalent conjugate composition.

1 39. The composition of claim 1, wherein the saponin comprises a
2 compound represented by the formula:



5 wherein, R is hydrogen or -C(O)H; R¹ is a member selected from the group
6 consisting of hydrogen, an optionally substituted C₁₋₂₀ aliphatic group, a saccharyl
7 group, and a group represented by the formula -C(O)-[C(R³)(R⁴)]_k-COOH, wherein
8 each R³ and R⁴ independently is a member selected from the group consisting of
hydrogen and optionally substituted C₁₋₁₀ aliphatic groups, and k is a number from 1

to 5; R² is a member selected from the group consisting of hydrogen, an optionally substituted C₁₋₂₀ aliphatic group, and a group represented by the formula
 $-(CH_2)_rCH(OH)(CH_2)_tOR^5$, wherein r and t are independently 1 or 2, and R⁵ is an optionally substituted C₂₋₂₀ aliphatic group, or a group represented by the formula



wherein j is 1-5, and R⁶ and R⁷ are independently selected from the group consisting of hydrogen and optionally substituted C₁₋₂₀ aliphatic groups; or a pharmacologically acceptable salt thereof.

40. The composition of claim 39, wherein R¹ is a mono- or disaccharide.

41. The composition of claim 40, wherein R¹ is a glucuronic acid group.

42. The composition of claim 39, wherein R, R¹ and R² are hydrogens.

43. The composition of claim 39, wherein R is hydrogen; R¹ is a saccharyl group, wherein the saccharyl group is a glucuronic acid group; and R² is hydrogen.

44. The composition of claim 39, wherein R is hydrogen; R¹ is represented by the formula $-C(O)-[C(R^3)(R^4)]_k-COOH$ wherein R³ and R⁴ are hydrogens and k is 2; and R² is hydrogen.

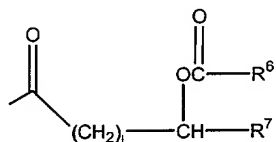
45. The composition of claim 39, wherein R is hydrogen; R¹ is a saccharyl group, wherein the saccharyl group is a glucuronic acid group; and R² is $(CH_2)_rCH(OH)(CH_2)_tOR^5$, wherein r and t are both 1, and R⁵ is an optionally substituted C₂₋₂₀ acyl group.

46. The composition of claim 43, wherein the glucuronic acid group is a β-D-glucuronic acid group.

47. The composition of claim 45, wherein $(CH_2)_rCH(OH)(CH_2)_tOR^5$ is a 1-O-acyl-sn-glyceryl group.

48. The composition of claim 47, wherein R⁵ is a member selected from the group consisting of acetyl, octanoyl, and tetradecanoyl groups.

1 49. The composition of claim 39, wherein R is hydrogen; R¹ is a saccharyl
2 group, wherein the sachharyl group is a glucuronic acid group; and R² is a group represented
3 by the formula:



4
5 wherein j is 1; R⁶ is an optionally substituted C₁₋₂₀ aliphatic group; and R⁷ is an
6 optionally substituted C₁₋₂₀ aliphatic group.

1 50. The composition of claim 49, wherein R⁷ is an optionally substituted
2 C₁₁ aliphatic group.

1 51. The composition of claim 1, further comprising at least one antigen.

1 52. The composition of claim 51, wherein the antigen is derived from the
2 group consisting of Herpes Simplex Virus type 1, Herpes Simplex virus type 2, Human
3 cytomegalovirus, HIV, Hepatitis A, B, C or E, Respiratory Syncytial virus, human papilloma
4 virus, Influenza virus, Tuberculosis, Leishmaniasis, T.Cruzi, Ehrlichia, Candida, Salmonella,
5 Neisseria, Borrelia, Chlamydia, Bordetella, Plasmodium and Toxoplasma.

1 53. The composition of claim 51, wherein the antigen is a human tumor
2 antigen.

1 54. The composition of claim 53, wherein the tumor antigen is derived
2 from a prostate, colon, breast, ovarian, pancreatic, brain, head and neck, melanoma, leukemia
3 or lymphoma cancer.

1 55. The composition of claim 51, wherein the antigen is a self antigen.

1 56. The composition of claim 55, wherein the self antigen is an antigen
2 associated with an autoimmune disease.

1 57. The composition of claim 52, wherein the autoimmune disease is type
2 1 diabetes, multiple sclerosis, myasthenia gravis, rheumatoid arthritis or psoriasis.

1 58. The composition of claim 1 comprising an aqueous formulation.

59. The composition of claim 58, wherein the aqueous formulation comprises one or more surfactants.

60. The composition of claim 59, wherein the aqueous formulation comprises one or more phospholipid surfactants.

61. The composition of claim 60, wherein the surfactant is selected from the group consisting of diacyl phosphatidyl glycerols, diacyl phosphatidyl cholines, diacyl phosphatidic acids, and diacyl phosphatidyl ethanolamines.

62. The composition of claim 60, wherein the surfactant is selected from the group consisting of dimyristoyl phosphatidyl glycerol (DPMG), dipalmitoyl phosphatidyl glycerol (DPPG), distearoyl phosphatidyl glycerol (DSPG), dimyristoyl phosphatidylcholine (DPMC), dipalmitoyl phosphatidylcholine (DPPC), distearoyl phosphatidylcholine (DSPC); dimyristoyl phosphatidic acid (DPMA), dipalmitoyl phosphatidic acid (DPPA), distearoyl phosphatidic acid (DSPA); dimyristoyl phosphatidyl ethanolamine (DPME), dipalmitoyl phosphatidyl ethanolamine (DPPE) and distearoyl phosphatidyl ethanolamine (DSPE).

63. The composition of claim 1, comprising an emulsion formulation.

64. The composition of claim 1, comprising a solid formulation.

65. The composition of claim 1, wherein the AGP and saponin are present in synergistically effective amounts.

66. The composition of claim 1, wherein the saponin and AGP are present in a weight ratio of saponin:AGP of from about 1000:1 to about 1:1000.

67. The composition of claim 1 further comprising a vaccine.

68. The composition of claim 2, wherein the saponin is selected from naturally obtained saponins, synthetically obtained saponins, saponin conjugates, saponin derivatives, and saponin mimetics.

69. The composition of claim 3, wherein the saponin is a quillaja saponin.

- 8
- 9 70. The composition of claim 69, wherein the saponin is QS-21.
- 10
- 11 71. The composition of claim 3, wherein the saponin is a saponin-lipophile
- 12 conjugate.
- 13
- 14 72. The composition of claim 71, wherein the saponin is GPI-0100.
- 15
- 16 73. The composition of claim 4, wherein the saponin is a quillaja saponin.
- 17
- 18 74. The composition of claim 73, wherein the saponin is QS-21.
- 19
- 20 75. The composition of claim 4, wherein the saponin is a saponin-lipophile
- 21 conjugate.
- 22
- 23 76. The composition of claim 75, wherein the saponin is GPI-0100.
- 24
- 25 77. The composition of claim 24, wherein the saponin is QS-21.
- 26
- 27 78. The composition of claim 24, wherein the saponin is GPI-0100.
- 28
- 29 79. The composition of claim 25, wherein the saponin is QS-21.
- 30
- 31 80. The composition of claim 25, wherein the saponin is GPI-0100.
- 32
- 33 81. The composition of claim 26, wherein the saponin is QS-21.
- 34
- 35 82. The composition of claim 26, wherein the saponin is GPI-0100.
- 36
- 37 83. The composition of claim 27, wherein the saponin is a quillaja saponin.
- 38
- 39 84. The composition of claim 83, wherein the saponin is QS-21.
- 40

41 85. The composition of claim 27, wherein the saponin is a saponin-
42 lipophile conjugate.

44 86. The composition of claim 85, wherein the saponin is GPI-0100.

46 87. A method of treating a mammal suffering from or susceptible to a
47 pathogenic infection, cancer or an autoimmune disorder comprising administering to the
48 mammal an effective amount of a composition according to claim 1.

50 88 A method of treating a mammal suffering from or susceptible to a
51 pathogenic infection, cancer or an autoimmune disorder comprising administering to the
52 mammal an effective amount of a composition according to claim 2

54 89 A method of treating a mammal suffering from or susceptible to a
55 pathogenic infection, cancer or an autoimmune disorder comprising administering to the
56 mammal an effective amount of a composition according to claim 30.

1 90. A method of enhancing the immune response in an animal which
2 comprises administering to the animal a composition according to claim 1.

4 91. A method of enhancing the immune response in an animal which
5 comprises administering to the animal a composition according to claim 2.

7 92. A method of enhancing the immune response in an animal which
8 comprises administering to the animal a composition according to claim 30.

1 93. A method of enhancing the immune response in an animal to an
2 antigen which comprises administering to the animal a composition according to claim 1 in
3 combination with an antigen.

5 94. A method of enhancing the immune response in an animal to an
6 antigen which comprises administering to the animal a composition according to claim 2 in
7 combination with an antigen.

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95. A method of enhancing the immune response in an animal to an

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antigen which comprises administering to the animal a composition according to claim 30 in

11

combination with an antigen.

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